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Strategies to improve the potential of transdermal devices by enhancing the skin permeation of therapeutic entities

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ABSTRACT

Although transdermal route of drug delivery displays numerous benefits over conventional strategies, this pathway is yet to presents its complete potential. The chief ground for this statement is ascribed to the presence of extremely packed outermost layer of skin called stratum corneum. This compactly packed barrier is selectively permeable and furnishes smaller and lipophilic molecules to diffuse into the deeper skin layers. Due to this only a few transdermal product is commercially available. So in order to guarantee the effective transport of drug molecules, it is necessary to break the stratum corneum layer. There are two acceptable methods to break the stratum corneum architecture- active strategy which comprises the application of external energy such as in electroporation, sonophoresis, iontophoresis etc. and passive strategy which involve the application of permeation enhancers, nanoparticles etc. This article comprehensively detail the active and passive methods employed in transdermal drug delivery systems to disrupt the stratum corneum bilayers.

Keywords: transdermal drug delivery, lipophilic molecules, permeation enhancers

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Introduction

Transdermal route of drug transport provides fascinating non-invasive approach compared to conventional strategies such as intravenous injection and oral routes. The chief benefit of transdermal strategy is the absence of first pass hepatic metabolism. In addition, transdermal route furnishes sustained delivery of therapeutic entities, ease of patch application, avoids the requirement of trained staff to administer drug, patch can be swiftly removed in the case of toxicity [1].

The conventionally used transdermal devices allow controlled delivery, but are employed to small lipophilic drug molecules ascribed to the barrier properties of the outermost layer of skin called stratum corneum (SC) [2]. The chief lipids present in the SC include fatty acids, wax esters, ceramides, cholesterol etc. Ceramides are the chief lipid groups and are pivotal to the organization of lipid architecture. The barrier behavior of SC is due to the lipid bilayers present in the intercellular spaces [1]. The permeation of skin can be improved by three main mechanisms such as by reorganizing physicochemical behavior of SC, by altering hydrating behavior of SC and by changing structures of proteins and lipids in the intercellular channels [3].

The progress of skin permeation enhancement approaches is likely to play a remarkable role in the development of transdermal pathway. Several skin permeation enhancement strategies have been introduced and studied to efficiently transport therapeutic entities across the skin. Reaearchers reported the so called passive and active approaches to enhance the permeation of both hydrophilic and lipophilic molecules across the skin [2].

Strategies to overcome skin barrier function

The poor permeability of mammalian skin ascribed to the compactly packed SC is the main hurdle in TD drug delivery. The principle challenges in TD research is to break the skin barrier properties. Over the last decades, there has been a significant interest in developing skin permeation enhancement techniques. Presently there are numerous enhancement techniques that can be employed to optimize TD drug delivery **(Fig. 1)**.

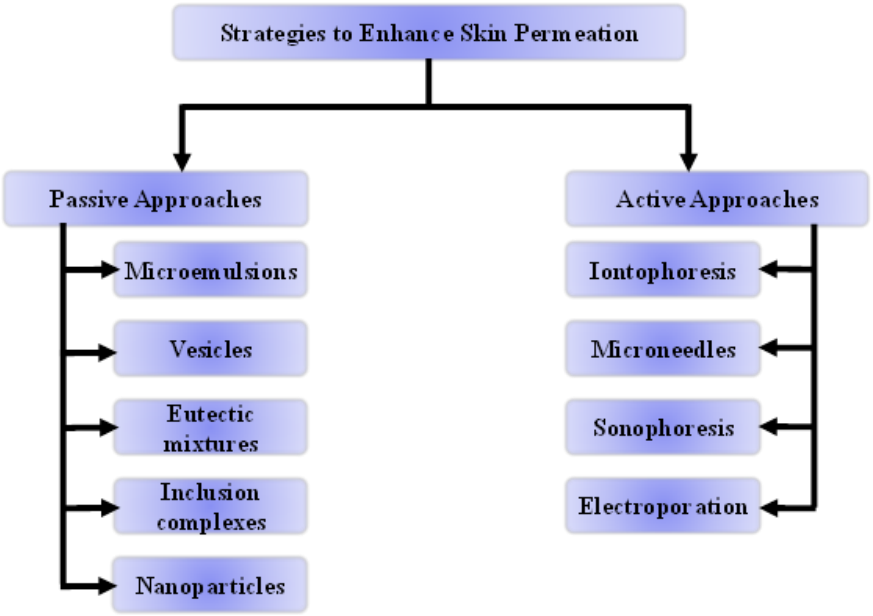

Fig. 1. Different approaches to overcome skin barrier function

1. Passive penetration enhancement strategies

The skin penetration mechanism in passive TD system is completely based on the diffusion of the therapeutic entities across the SC layers. Latest approaches which are presently under research ranging from chemical penetration enhancers which breaks the SC barrier function by intensifying the drug diffusion across the SC layers or improving the solubility of drugs in the skin to advanced strategies, which comprises the magnification of this idea to the development of nanoparticles, inclusion complexes, vesicle formulations etc.

1.1. Microemulsions

Microemulsions are stable and clear dispersion comprising of oil, surfactant and aqueous phase, commonly in combination with a co-surfactant. Recently microemulsions have been widely investigated in TD applications due to their thermodynamic stability, easy and inexpensive preparation, increased bioavailability, small droplet size and high solubilization capacity for both lipophilic and hydrophilic drug molecules [4].

The frequently studied skin penetration enhancers that have been employed as oil phase of TD microemulsion are saturated and unsaturated fatty acids. Aungst and coworkers investigated the TD delivery of naloxone using several vehicles such as fatty acids, sulfoxides, alcohol etc and revealed that the vehicles with an unsaturated C_{10}-C_{12} and a polar head and vehicles with C_{18} alkyl group like oleic acid, observed to be the optimal formulations. Compared to trans configuration, the unsaturated cis configuration can effectively disturb the compactly packed SC lipid layers [5]. Due to the hydrophobic nature of SC layers, the fatty acid can effectively interact with lipid bilayers and disturb it by producing separate domains which ultimately enhances skin permeability [6]. On the other hand surfactants such as phospholipids, polysorbates, azones, polyglycerol fatty acid esters, dioctyl sodium sulphosuccinate etc can effectively perturb SC layers. It is necessary to stress that water is used as aqueous phase in most of the formulations [4]. The skin permeation profile of microemulsons is remarkably higher upon compared to conventional formulations such as creams and losions.

1.2. Vesicles

Vesicles function as both drug carrier to transport encapsulated drug across the SC layers and skin penetration enhancer to break barrier function. Liposomes and niosomes are the vesicular platforms which have acquired ample attention to facilitate TD drug delivery. Literature stated that in certain cases liposomes and niosomes are retained in the upper layer of SC and cannot penetrate into deeper skin layers to obtain desired therapeutic effect [7].

Transferosomes are a unique class of liposomes, comprising of phosphatidylcholine and an edge activator and possess significant elasticity compared to conventinal liposomes. It can encapsulate therapeutic entities with different range of solubility as they contains both hydrophilic and hydrophobic moities. They bypass the SC layer by squeezing themselves along the intercellular sealing lipids of SC [8]. Furthermore transferosomes are biocompatinle, non-toxic and possess high encapsulation efficiency. Kong et al prepared HA modified trnsferosomes to transport doxorubicin across the skin and reported that the device could potentially penetrate into deeper skin layers, furnishing a new perspective for tumor metastatis therapy [9]. Ethosomes are another catergory of vesicles prepared from phospholipids, ethanol and water, which provide remarkably higher TD flux compared to liposomes. Ethanol present in ethosomes function as a penetration enhancer and transport drug across intercellular lipids [10].

1.3. Eutectic mixtures

Eutectic mixture is a combination of two or more components which normally do not combine to form a new compound; however which at particular ratios give a system with lower melting point than the components mixed. Literature disclosed that the melting point of a drug is inversely related to its lipophilicity and solubility in lipids. Hence lowering of melting point of drugs by the formation of an eutectic mixture increases its lipid solubility and finally enhances TD flux [11].

The eutectic mixture enhances the TD flux by two discrete mechanisms. One is the development of a low melting mixture with the therapeutic entity which enhances its partition across the SC layers. Other is the direct perturbation of SC architecture which additionally improves the skin permeability [12]. Yuan et al remarkably lowered the melting point of ibuprofen and ketoprofen by eutectic

mixture formation in presence of aqueous isopropyl alcohol and enhanced their skin permeability [13]. The research group of Barry prepared eutectic mixtures between ibuprofen and seven terpenes including thymol, cineol etc. They found that the TD flux of ibuprofen across the skin from the eutectic system was significantly higher compared to saturated aqueous solution [14].

1.4. Inclusion complexes

Inclusion complex is a species in which one compound called the "host" possess an internal cavity into which another compound the "guest" can seat. The distinct architecture of βCD with a hydrophobic cavity and a hydrophilic exterior surface permits the formation of inclusion complex. Modified βCD is an interesting TD drug delivery platform as they enhance the skin permeability by two mechanistic pathways. βCD improves the solubility of drug molecules, producing a greater driving force for piercing SC layers. The interaction of βCD with lipid bilayers also breaks skin barrier properties. In addition to furnishing exceptional permeability, βCD complexation significantly reduces the drug induced irritation [15]. Felton et al reported that hydroxypropyl-βCD remarkably enhanced the aqueous solubility of oxybenzone and improved its skin permeability [16]. Avobenzone- hydroxypropyl-βCD complexation was reported by Yang et al and skin permeability studies revealed that the TD flux enhanced with increasing the concentration of hydroxypropyl-βCD [17].

1.5. Nanoparticles

In the last few decades nanoparticles have been widely studied for several pharmaceutical applications as they furnish sustained drug release, enhance the stability of drug molecules by physical or chemical means and offer targeted therapy [18]. Interestingly nanoparticles have gained significant attention as TD carriers due to their ability to penetrate skin layers as a function of size, surface charge and shape. It is regarded that nanoparticles pierce the skin by three routes:- intercellular pathway through corneocytes, intercellular routes through lipids or dermal architecture such as hair follicles [19].

The most widely employed nanoparticles for TD applications include metal nanoparticles, polymeric nanoparticles, nano-emulsions, dendrimers etc [18]. Natural polymeric nanoparticles such as CS, alginic acid and albumin nanoparticles have been widely investigated as TD drug delivery platform. Nevertheless natural polymers are replaced by synthetic polymers to furnish high purity and consistent drug release pattern. Sheihet et al prepared ABA triblock polymer nanospheres from polyethylene glycol, suberic acid and desaminotyrocyl-tyrosine alkyl ethers. *In vitro* permeation test disclosed that these nanospheres delivered model drug molecules nine times more to deeper skin layers compared to reference device [20].

Dendrimers are complex molecules which have been extensively used to develop TD formulations ascribed to its nanometric size and narrow polydispersity. Priyanka et al in a review stated that dendrimers are employed for the TD delivery of non-steroidal anti-inflammatory, antimicrobial, antihypertensive and anticancer drugs [21]. Dendrimers enhance the TD flux by temporarily perturbing the skin layers to furnish a diffusion pathway for penetrating molecules. Furthermore its globular shape enhances its capacity to break barrier functions than linear shaped molecules [22]. The investigation of Hong's group revealed that poly(amidoamine) dendrimers produces nanosized openings on lipid bilayers as a result of strong lipid-dendrimer interaction [23].

Metallic nanoparticles such as gold nanoparticle (GNP), silver nanoparticle, titanium nanotube (TNT) etc received ample attention in TD drug delivery due to their substantial effect on local penetration in SC layers. Tak et al studied the shape dependent skin penetration behavior of silver nanoparticles. *In vivo* skin permeation studies have shown that rod shaped nanoparticles demonstrated the highest skin permeability followed by spherical and triangular nanoparticles. These outcomes indicated that the intercellular pathway plays a significant role in enhancing the skin permeability and not the follicular route [24].

In addition to the detailed strategies skin permeability can also be enhanced using super loaded formulations, coacervation effect etc [12]. An efficient method to enhance TD flux is by enhancing the concentration of dissolved drugs without causing any damage to skin tissue. In coacervation techniques oppositely charged species forms pair, dissociates in epidermis and releasing the parent molecules [25]. Efforts are in progress to fabricate potential TD platforms that provide sufficient therapeutic efficiency without generating any health issues.

2. Active penetration enhancement strategies

2.1. Iontophoresis

TD iontophoresis is a needleless approach in which a small electric current is used to transport therapeutic entities across the skin. It is a programmable system in which the rate of transport of drug molecules could be controlled by the fine-tuning of the applied electric current. In this technique only a feable current below 500 $\mu A/cm^2$ of skin is applied to avoid pain, burn and irritation caused by the application of electric current. Iontophoresis enhances the skin permeability by distinct mechanisms such as electroosmosis, electrophoresis and increasing the skin porosity [26].

Nevertheless the potential of iontophoresis to improve the TD flux of non-polar drugs is unsatisfactory due to the absence of charge and poor solubility in water [27]. The passive TD strategy of proteins and peptides is less efficient as they are charged at physiological pH. However iontophoresis significantly enhances the TD flux of charged species [28]. Literature stated that charged species generally select the pathway of least electrical resistance in the skin and the route is assumed to be the sweat glands or hair follicles [29]. In iontophoresis the anionic drugs are place under cathode and cationic drugs under anode. When a feable electric current is supplied, the drugs are repelled into the skin and finally penetrates through different skin layers to reach the systemic distribution. Furthermore iontophoresis has been employed for the TD delivery of steroids, anaesthetics, retenoids, anti-inflammatory drugs etc.

2.2. Microneedles

TD microneedle patches have been substantially investigated in the last few years due to their ease of application, high drug loading, painless administration and potential drug delivery. The fabrication of microneedle should be in such a way that the needle possess sufficient length to pierce into the dermis, but should be narrow to prevent the stimulation of dermal nerves. Microneedle therapy remarkably improves the penetration of drug molecules across the skin. When applied on skin, the narrow needle can efficiently puncture the SC layers and a portion of the epidermis, producing micron-sized holes which promote the delivery of drug molecules to dermal micro circulation.

The substances employed to fabricate micronnedles are silicon, polymers and metals. Hollow microneedle array is a special type of patch that permits the TD transport of drug molecules across the skin via the injection of the formulations through the adhered hollow device. Coated microneedle is another TD patch fabricated by coating solid microneedle with a formulation of drug before inserting into skin surface. The coated microneedle patches heve been used for the TD delivery of several molecules including proteins, DNA and peptides [30]. Dissolving microneedles are intersting catergory of TD device. The water soluble polymeric microneedles prepared from PVA, gelatin, HA, poly(vinyl pyrrolidone) and carboxymethylcellulose when applied on skin, they swiftly dissolve upon exposure with water and hence avoids the danger of needles staying in the skin. The fabrication of microneedle patches presently faces certain issues including the harsh processing conditions, which restricts the category of drugs that can be employed. Furthermore, the application of microneedle patches produce microscopic holes, which sometimes results in bacterial infections. There are still milestones to be acquired to develop a more patient friendly microneedle patch with controlled drug delivery [31].

2.3. Sonophoresis

The ultrasound mediated TD drug delivery at frequencies in the range of 20 KHz – 16 MHz and intensity upto 14 W/cm^2 is referred as sonophoresis. The TD flux is remarkably higher at low frquency range (20-100 kHz) than at high frequency [32]. The skin penetration enhancement effect of ultrasound is described by two mechanisms- thermal effect and cavitational effects. When skin is treated with ultrasound, the absorption of energy results in local temperature increase which results in enhanced skin permeability. The research group of Gay evaluated the role of ultrasound frequency on the TD delivery of mannitol and found that the application of low frequency ultrasound (20 KHz) increased the temperature by around 20 ^{0}C and enhance the TD flux by approximately 35 fold. However they also reported that the enhancement effect is also ascibed to another mechanism called cavitation [33]. Cavitation means the generation of cavities and disruption of pre-existing gas bubbles in a liquid medium. The violent growth and collapse of bubbles upon ultrasound propagation produces shock waves, which creates structural changes in SC layers. This alteration of SC architecture generates channels for the facile diffusion of drug molecules [34]. The size and cost of the ultrasound equipments is the principal challenge in the sonophoresis. Furthermore the safety of ultrasound application should be throughly investigated through further research.

2.4. Electroporation

Electroporation refers to the temporary disruption of SC layers and further enhancement in TD drug delivery following the influence of electric pulse. It has been used for the efficient TD transportation of drugs like metroprolol and fentanyl, macromolecules like heparin, oligonucleotides and peptides. Enhancement in electroporation mediated TD delivery between one and four order of magnitudes have been acquired, depending on the size and solubility of drugs and strength of the applied voltage pulses.

The important characteristics of electroporation consists enhanced TD flux for a variety of drug molecules, quick responsive TD delivery and modulation of delivery by regulating the physicochemical behavior of reservoir and electrical parameters [35]. Several strategies have been employed to evaluate the skin tolerance of electroporation. Ultrastructural investigation and clinical tests revealed that the overall alteration of the skin architecture upon skin electroporation are gentle and reversible [35].

2.5. Other approaches

Pressure wave produced by intense laser radiation is one of the recent strategy which can enhance the skin permeability. The pressure wave only permeabilizes the SC layer and the transport of therapeutic entities occur by diffusion under the concentration gradient through the channels created by the pressure waves [36]. Magnetic field have also been used to overcome the skin barrier properties. Literature stated that magnetic field enhanced the TD delivery of drug molecules including terbutaline sulfate, salbutamol sulfate etc [37](Murthy et al., 2010). The investigation of Krishnan and coworkers disclosed that the TD drug delivery was enhanced by the application of electromagnetic field of 5.0 mT and is ascribed to the modulation of SC permeability [38]. Needleless injector is an attractive TD drug delivery platform which offer less pain than hypodermal injection. This technique is used for the delivery of peptides and proteins across the skin [39].

Conclusions

In this article the passive and active methods to vanquish the SC layers are detailed. Passive strategies such as microemulsions, vesicles, eutetic mixtures, inclusion complex and nanoparticle displays excellent potential to enhance the transport of therapeutic entities across the skin. Active strategies includes iontophoresis, microneedles, sonophoresis and electroporation, could effectively disrupt lipid layers of skin and facilitates the transport of drug molecules. This article could assist researchers to accelerates the development of transdermal products.

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